The claims on the replacement pages correspond to the original PCT claims as follows:

PCT Claims	New Claims
1-61	1-61

Certain of the claims have been amended in response to the Written Opinion. The claims that have been amended are claims 9, 32, 34, 35, 43, and 51.

REMARKS

On the basis of newly presented claims 1-61 reconsideration of this application is requested. Claims 1-61 as submitted are fully supported by the specification as filed, as established by the following remarks.

Claims 9, 32, 43, and 51 are amended to recite "IαIp protein", deleting the potentially ambiguous term "complex." These claims still refer to the same protein species.

Claim 34 is amended so that it is consistent with claim 32 from which it depends.

Claim 35 is amended to add the limitation "the protein being expressed by the cell such that the protein is processed and glycosylated, if necessary, so that its *in vivo* function is substantially preserved after isolation of the protein." The scope of this limitation is present in original claim 1, and thus can be added to claim 35.

Accordingly, the specification complies with PCT Rule 66.2(a)(v) with respect to the amended claims. It is believed that these claims, as amended, clarify the patentable subject matter of the present invention without raising any new issues.

In the Written Opinion, claims 9, 19-20, 27-28, 30-31, 33-34, 37, 43, and 46-61 were stated to meet the criteria set out in PCT Article 33(2) for novelty, because a single prior art reference did not teach or fairly suggest the claimed invention.

Claims 1-8, 10-18, 22-26, 29, 35-36, 39-42, and 44-45 were stated to lack novelty under PCT Article 33(2) as being anticipated by N. Kobayashi et al., "Improvement in the Differentiated Hepatic Phenotype of Immortalized Human Hepatocytes by Adenovirus Mediated p21 Gene Transfer," ASAIO J. 48: 355-359 (2002) ("Kobayashi et al. (2002)").

Claims 9, 19-20, 27-28, and 43 were stated to lack an inventive step under PCT Article 33(3) as being obvious over Kobayashi et al. (2002) in view of U.S. Patent No. 6,517,830 to Lollar et al. ("Lollar et al. '830").

Claims 32 and 33 were stated to lack an inventive step under PCT Article 33(3) as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830 and further in view of B.K. Lucas et al., "High-Level Production of Recombinant Proteins in CHO Cells Using a Dicistronic DHFR Intron Expression Vector," Nucl. Acids Res. 24: 1774-1779 (1996) ("Lucas et al. (1996)").

Claim 30 was stated to lack an inventive step under PCT Article 33(3) as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830, further in view of Lucas et al. (1996) and still further in view of J.B. Mills et al., "Induction of Drug Metabolism Enzymes and MDR1 Using a Novel Human Hepatocyte Cell Line," J. Pharmacol. Exp. Therap. 309: 303-309 (2004) ("Mills et al. (2004)").

Although, in the Supplemental Box of the Written Opinion, it was stated that the opinion as to inventive step was negative with respect to claims 1-61, specific rejections were made only with respect to claims 1-20, 22-30, 32-33, 35-36, and 39-45. No specific rejections were made with respect to claims 21, 31, 34, 37,

and 38. Clarification is requested. The teachings of the references are addressed below with respect to the subject matter of claims 21, 31, 34, 37, and 38. However, the addressing of the teachings of the references with respect to claims 21, 31, 34, 37, and 38 is not intended to be treated as an admission that a rejection of these claims on the grounds of lack of inventive step was proper or should in fact have been made. This issue is merely addressed for the sake of completeness.

Claims 1-61 were also stated to meet the criteria set out in PCT Article 33(4) for industrial applicability.

Claims 9, 21, 34, and 43 were objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 on the grounds that the claims were stated to be indefinite.

Claims 46-61 were objected to as lacking clarity under PCT Rule 66.2(a)(v) on the grounds that the claims were not fully supported by the specification for *in vivo* therapy.

As detailed below, all of the claims as amended that are currently under consideration meet the standards of PCT Article 33(2) for novelty and of PCT Article 33(3) for inventive step. In other words, all of these claims are novel and non-obvious.

With respect to the objections raised by the Examiner with regard to claims 9, 21, 34, and 43 under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 on the grounds that the claims were stated to be indefinite, Applicant has amended claim 9 and 43. Claim 9 is amended so that it reads: "The method of claim 1 wherein the protein is an IαIp protein." Similarly, claim 43 is amended so that it reads: "The cell of claim 35 wherein the plasma protein is an IαIp protein." Many naturally-occurring proteins are actually complexes of multiple subunits, held together by noncovalent bonds. An example is human hemoglobin, which consists of two α

chains and two β chains. There should be no ambiguity in the designation of "IαIp protein" in this claim. In fact, the term "IαIp proteins" (without "complex") is used in the specification at page 26, line 22. Therefore, the Examiner is respectfully requested to withdraw this objection.

For consistency, other claims reciting "IαIp protein complex" are also amended to read "IαIp protein." This includes claims 32 and 51.

With respect to the designation of "control element" in claim 21, this term is well understood by those of ordinary skill in the art as referring to nucleic acid segments that control the expression of genes, such as promoters or enhancers. This term is used at page 23, lines 24-29 of the specification in exactly this manner. Therefore, there is no ambiguity in this term, and the Examiner is respectfully requested to withdraw this rejection.

With respect to the objection to claim 34, claim 34 is amended so that it reads "eukaryotic cell" instead of "hepatocyte." As amended, claim 34 is now consistent with claim 32, from which it depends. The Examiner is therefore respectfully requested to withdraw this rejection.

With respect to the objection to claims 46-61 as lacking clarity under PCT Rule 66.2(a)(v) on the grounds that the claims were not fully supported by the specification for *in vivo* therapy, Applicant, as detailed below, replies that the specification fully supports the scope of the claims.

Claims 46-61 are fully supported by the specification for *in vivo* therapy because one of ordinary skill in the art has been provided with sufficient information to enable the use of plasma proteins and compositions according to the present invention for therapy. Because these proteins are native human proteins, they will not be immunogenic in the vast majority of instances, and so there should be no

problem stemming from an immune response to the administered protein, a common problem arising from therapy with xenogeneic proteins, such as murine antibodies.

The use of a recombinant protein does not, in and of itself, give rise to an immunogenic response as long as the protein that is actually administered is one that is identical in its structure, or sufficiently close to the native protein, so that no immune response is triggered. A typical example is recombinant human insulin, which can be administered safely to diabetic patients who have or may develop an immune response against bovine or porcine insulin.

There is absolutely no evidence that any of the proteins of the present invention would be subject to degradation or removal before a therapeutic effect had been exerted. If there is some degradation or removal, this would be relevant only for the degree of the therapeutic effect and could be countered by changing the quantity administered, the temporal pattern of administration (number or frequency of doses), or the route of administration. These changes could be readily accomplished by one of ordinary skill in the art.

Many recombinant proteins are now commonly used as *in vivo* therapeutics. Examples include hematopoietic factors such as recombinant granulocyte colony-stimulating factor (filgrastim), recombinant granulocyte-macrophage colony-stimulating factor, and recombinant erythropoietin. These are frequently used and are well-tolerated; their therapeutic benefits are widely recognized.

The specification does provide sufficient teaching to enable one skilled in the art to use the claimed invention for therapy. This is found at pages 30-31 of the specification. The preparation of pharmaceutical compositions from substances having an active therapeutic effect is well known in the art and does not require undue experimentation. Therefore, the statement that "the level of unpredictability in the art of *in vivo* methods of treating disease with a recombinant/cultured protein is high enough, so that undue experimentation is necessary to practice the claimed method

and to produce and utilize the claimed pharmaceutical compositions" is not consistent with the currently-understood utility of recombinant proteins for therapeutic purposes. Therefore, the Examiner is respectfully requested to withdraw this objection.

Claims 1-8, 10-18, 22-26, 29, 35-36, 39-42, and 44-45 were stated to lack novelty under PCT Article 33(2) as being anticipated by Kobayashi et al. (2002).

The Examiner is respectfully requested to withdraw this objection on the grounds of lack of novelty because Kobayashi et al. does not disclose the subject matter of the claimed invention. Specifically, claim 1 requires: "the protein is expressed such that the protein is processed and glycosylated, if necessary, so that its *in vivo* function is substantially preserved after its isolation." This limitation is not met by the teachings of Kobayashi et al. (2002).

Kobayashi et al. (2002) is directed to the introduction of a recombinant vector encoding the regulatory protein p21 into one particular line of immortalized human hepatocyte cells designated NKNT-3. This regulatory protein is not, in and of itself, a protein that would be isolated from the cells or used for therapy. Rather, it functions to regulate the transition from the G1 phase to the S phase of the cell cycle. Kobayashi et al. (2002) claimed to show "improvement of protein expression of CYP 3A4 and CYP 2C9" (abstract).

However, Kobayashi et al. (2002) does not show in fact that "the protein is expressed such that the protein is processed and glycosylated, if necessary, so that its *in vivo* function is substantially preserved after its isolation," as required for anticipation of claim 1. Other claims have substantially similar language.

All that Kobayashi et al. (2002) shows is that there is "improvement of protein expression of CYP 3A4 and CYP 2C9." These cytochrome P450 isoforms are not glycosylated. As reported in F.P. Guengerich, "Cytochrome P450: What Have We Learned and What Are the Future Issues," Drug Metab. Rev. 36: 159-197 (2004) ("Guengerich (2004)"), attached hereto as Exhibit A: "Glycosylation has not been

found in the cases it has been examined. The only report of glycosylation involves P450 19A1 (the aromatase), except for a small amount of sugars in early preparations of rabbit P450s. Presumably, extensive posttranslational modification does not occur because catalytically active P450s can be expressed in bacteria, including P450 19A1." (Guengerich (2004), p. 168 (citations omitted)). The aromatase is distinct from the P450 isoforms examined in Kobayashi et al. (2002), which were CYP 3A4 and CYP 2C9.

Moreover, even the activity of the P450 isoforms CYP 3A4 and CYP 2C9 were not examined in Kobayashi et al. (2002). The Western blotting performed merely detected the quantity of protein and did not monitor or measure the enzymatic activity of the protein.

In summary, Kobayashi et al. (2002) does not teach or disclose how the proteins can be actually isolated from the cultured cells in active and, if necessary, in properly glycosylated form.

Therefore, there is no disclosure in Kobayashi et al. (2002) that proteins whose genes are introduced by exogenous vectors are expressed in active form, including glycosylation where required. The example of Kobayashi et al. (2002), dealing with expression of a transcription factor, cannot be generalized without more information. As such, it does not, expressly or inherently, anticipate the subject matter of these claims.

The foregoing discussion makes it clear that Kobayashi et al. (2002) anticipates none of the claims of the present application, including claims 1-8, 10-18, 22-26, 29, 35-36, 39-42, and 44-45. However, for additional reasons, claims 3 and 7 are not anticipated by Kobayashi et al. (2002).

In particular, there is no teaching in Kobayashi et al. (2002) of the production of "a protein that is not naturally produced by human hepatocytes" (claim 3). There is also no teaching in Kobayashi et al. (2002) of the production of any of

the proteins recited in claim 7: Factor VIII, Factor IX, human growth hormone (hGH), α-1-antitrypsin, or a growth factor.

Accordingly, the Examiner is respectfully requested to withdraw the objection to claims 1-8, 10-18, 22-26, 29, 35-36, 39-42, and 44-45 for lack of novelty as anticipated by Kobayashi et al. (2002).

Claims 9, 19-20, 27-28, and 43 were stated to lack an inventive step under PCT Article 33(3) as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830. Lollar et al. '830 is cited for the use of adenovirus-based vectors to express plasma proteins. However, this is performed, not in hepatocytes, but in liver endothelial sinusoidal cells (LSECs), a different cell type, with different morphology and a different pattern of protein expression. The teachings of Lollar et al. '830 do not remedy the deficiencies of Kobayashi et al. (2002), as it does not show that these vectors can be used in hepatocytes for the expression of proteins such that the proteins are properly processed.

Therefore, the Examiner is respectfully requested to withdraw the objection to claims 9, 19-20, 27-28, and 43 as lacking an inventive step as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830.

Claims 32 and 33 were stated to lack an inventive step under PCT Article 33(3) as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830 and further in view of Lucas et al. (1996). Lucas et al. (1996) is cited for the high level production of recombinant proteins in CHO cells using an expression vector. However, according to the teachings of Lucas et al. (1996), the vectors used in Lucas et al. (1996) were designed specifically to work in CHO cells and to bear a selectable marker for those cells. The vector used in Lucas et al. (1996) is not used in the methods and the transformed cells of the present invention. The fact that other vectors can be used does not mean that there is a sufficiently high probability of success for expression of proteins normally expressed in hepatocytes in cells such as

CHO cells using the same vectors as in hepatocytes. There is not a sufficient probability of success taught by the references.

Therefore, the Examiner is respectfully requested to withdraw the objection to claims 32 and 33 as lacking an inventive step as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830 and further in view of Lucas et al. (1996).

Claim 30 was stated to lack an inventive step under PCT Article 33(3) as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830, further in view of Lucas et al. (1996) and still further in view of Mills et al. (2004). However, Mills et al. (2004) is not properly prior art with respect to the claims of this application. This application claims a priority date of October 10, 2003, the filing date of United States Provisional Application Serial No. 60/510,509. Mills et al. (2004) was not published until January, 2004; the citation of the 2003 date is erroneous. A close inspection of Mills et al. (2004) reveals that it was received by the journal on October 15, 2003 and accepted on December 5, 2003. It would not have been possible for a journal article received by the journal in October 2003 to have been published by the same journal in January 2003. The written-in date of "January 13, 2003" at the top of the copy of the document provided with the Written Opinion is therefore erroneous and must have been correctly "January 13, 2004." As such, it is later than the claimed priority date and is not prior art.

Accordingly, the Examiner is therefore respectfully requested to withdraw the objection to claim 30 as lacking an inventive step as being obvious over Kobayashi et al. (2002) in view of Lollar et al. '830, further in view of Lucas et al. (1996) and still further in view of Mills et al. (2004).

The Examiner is therefore respectfully requested to provide an International Preliminary Examination Report (IPER) in which these amendments and remarks are taken into account and in which the objections recited in the Written Opinion of July 29, 2005 are withdrawn.

Respectfully submitted,
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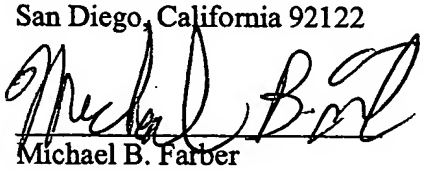
Date: October 28, 2005

By: 

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